## Title

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# Is High-dose Radiation Therapy Associated With Early Revision Due to Aseptic Loosening in Patients With a Sarcoma of the Lower Extremities Reconstructed With a Cemented Endoprosthesis?

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## Abstract

*Background* The durability of endoprostheses after limb salvage surgery is influenced by surgical factors (resection length, implant location, and residual bone quality), implant design (modular versus custom design, rotating versus fixed hinge, coating, collars, and the use of cross pins), and host factors (patient's immune status, activity levels, and age). In general, radiation therapy increases the risk of fractures, infection, delayed wound healing, and impaired osseointegration. Several studies have shown exposure to radiation to be associated with higher endoprosthesis revision rates and higher periprosthetic infection rates, but results are inconsistent. Although radiation therapy is not routinely used in the treatment of many bone sarcomas in current practice, it is still used in high doses after resection and prosthetic reconstruction in patients who have Ewing sarcoma with close or positive margins and in patients with soft tissue sarcoma. It is also used in varying doses after prosthetic reconstruction in patients with myeloma or bone metastasis after resection of periarticular destructive tumors. These patients may be at an increased risk of complications due to their radiation exposure, but this is a difficult question to study given the rarity of these diagnoses and poor overall survival of these patients. We therefore leveraged a large, longitudinally collected, 40-year endoprosthesis database that included patients who received radiation to the extremity for many bone and soft tissue sarcomas to investigate the association between preoperative or postoperative radiation therapy and endoprosthesis survival.

*Questions/purposes* (1) Is receiving preoperative or postoperative radiation therapy in low or high doses for the treatment of bone or soft tissue malignancy of the lower extremities associated with decreased implant survivorship free from amputation or revision due to any cause? (2) Is receiving preoperative or postoperative radiation therapy in low or high doses for the treatment of bone or soft tissue

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Ethical approval for this study was obtained from the University of California Los Angeles Office of the Human Research Protection Program (IRB#10-001857-AM-00031).
This work was performed at the David Geffen School of Medicine, University of California, Los Angeles, CA, USA.

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malignancy of the lower extremities associated with decreased implant survivorship free from revision specifically due to aseptic loosening? (3) Is receiving preoperative or postoperative radiation therapy for the treatment of Ewing sarcoma of the femur specifically associated with decreased implant survivorship free from revision specifically due to aseptic loosening?

*Methods* This was a retrospective, comparative study using our institution's database of 822 endoprostheses. Between 1980 and 2019, we treated 541 patients with primary cemented endoprostheses of the extremities. Of those patients, 8% (45 of 541) were excluded due to unknown radiation status, 3% (17 of 541) because of prior failed allograft, 15% (83 of 541) due to metastatic disease from a carcinoma, 1% (6 of 541) due to a nononcologic diagnosis, 4% (20 of 541) due to benign tumor diagnosis, 16% (87 of 541) due to upper extremity tumor location, 9% (49 of 541) due to not receiving chemotherapy, and 3% (14 of 541) due to expandable prostheses. Of the remaining 220 patients, 6% (13) were considered missing because they did not have 2 years of follow-up and did not reach a study endpoint. No patients had surgery within the last 2 years of the study end date. In all, 207 patients met inclusion criteria and were eligible for analysis. Patients who had received radiation to the lower extremities at any point in their treatment course were included in the radiation group and were compared with patients who did not receive radiation. For patients where radiation dose was available, the radiation group was subdivided into a low-dose (≤ 3000 cGy) and high-dose (> 3000 cGy) group. Revision surgery was defined as any surgery necessitating removal or replacement of the tibial or femoral stem. The complications necessitating revision or amputation were poor wound healing, aseptic loosening, implant breakage, deep infection, and tumor progression. The primary outcome of interest was implant survival free from revision or amputation due to any cause. The secondary outcome of interest was implant survival free from revision or amputation specifically due to aseptic loosening. The Kaplan-Meier survivorship curves were generated with implant survival free from revision or amputation as the endpoint and patient death as a competing risk. A log-rank test was used to identify differences in survivorship between the patients who received radiation and those who did not. Multivariate regression was used to identify factors associated with decreased implant survival. An odds ratio was used to determine relative effect size among the factors associated with decreased implant survival.

*Results* The mean implant survival time for patients who did not receive radiation was 18.3 years (95% confidence interval [CI] 15.4 to 21.3) whereas the mean implant survival time for patients who received low- and high-dose radiation were 19.1 years (95% CI 14.5 to 23.7; p = 0.59) and 13.8 years (95% CI 8.2 to 19.5; p = 0.65), respectively. The mean implant survival free from revision for aseptic loosening for patients who did not receive radiation was 27.1 years (95% CI 24.1 to 30.1) whereas the mean implant survival for patients who received low- and high-dose radiation were 24.1 years (95% CI 19.1 to 29.1; p = 0.34) and 16.4 years (95% CI 10.6 to 22.2; p = 0.01), respectively. Patients who received high-dose radiation had decreased 5-year implant survivorship free from amputation or revision due to aseptic loosening (73% [95% CI 44% to 89%]) compared with patients who did not receive radiation (95% [95% CI 90% to 99%]; p = 0.01). For patients treated for Ewing sarcoma of the femur, the 5-year implant survival free from amputation or revision due to aseptic loosening for patients who did not receive radiation (100% [95% CI 100% to 100%]) was no different compared with patients who received radiation (71% [95% CI 35% to 90%]; p = 0.56).

*Conclusion* The results of this study may apply to scenarios where radiation is used, such as Ewing sarcoma with positive margins or local recurrence and after prosthetic reconstruction in patients with myeloma or bone metastasis after resection of periarticular destructive tumors. Surgeons may consider closer monitoring for early clinical and radiographic signs of aseptic loosening in patients who received high-dose radiation. These patients may also benefit from constructs that have increased resistance to aseptic loosening such as cross-pin or side plate fixation. The association between radiation and aseptic loosening should be further studied with larger studies with homogeneity in tumor diagnosis and prosthesis. The dose-dependent relationship between radiation and bone-related complications may also benefit from controlled, laboratory-based biomechanical studies.

*Level of Evidence* Level III, therapeutic study.

## Introduction

Since the 1980s, limb salvage surgery has replaced amputation as the main treatment of extremity bone and soft tissue tumors. Advantages of tumor resection and reconstruction with an endoprosthesis include early weightbearing, durability, and better functional results than amputation [6, 16, 28, 30]. External beam radiation therapy is not routinely used for primary bone tumors but may be performed preoperatively for Ewing sarcoma or postoperatively because of inadequate surgical margins or local recurrence. Although radiation therapy may be used to treat the primary malignancy in certain patients, it adversely affects tissues in the radiation field and is associated with several complications including fracture, osteonecrosis, growth plate arrest in skeletally immature children, delayed fracture healing, periprosthetic infection, decreased postoperative functional scores, and impaired osseointegration [2, 10, 18, 20, 22, 23, 32, 35, 37]. The proposed mechanism of these harmful effects on bone specifically is that radiation causes impaired bone healing through decreased proliferation of osteoblasts and impaired extracellular matrix formation [11, 12].

Radiation-induced bone damage is dose dependent, with impaired healing observed at doses greater than 3000 cGy and severe damage or bone death at doses greater than 5000 cGy [38]. Radiation also causes deleterious effects on soft tissue, which may cause functional compromise.

Because of the effects of radiation, patients exposed to high doses for the treatment of their bone or soft tissue tumor may be at higher risk of complications after reconstruction with an endoprosthesis. Although several studies have looked at endoprosthesis survivorship after radiation therapy, the results have been inconclusive, with some reporting decreased revision-free survival and higher rates of infection whereas others have found no association [9, 15, 16, 22, 23, 27, 33]. The link between radiation therapy and aseptic loosening of the endoprostheses is even more unclear. A recent meta-analysis in THA identified a history of pelvic radiation to be associated with increased rates of aseptic loosening in both uncemented and cemented implants [26]. Although radiation therapy is not routinely used in the treatment of bone sarcomas, it is used in varying doses after prosthetic reconstruction in patients with myeloma or bone metastasis after resection of periarticular destructive tumors [3, 4, 14, 17, 21]. It is also used in high doses after resection and prosthetic reconstruction in patients with Ewing sarcoma with close or positive margins [8, 34]. These patients may be at an increased risk of prosthetic complications due to their radiation exposure, but this is a difficult question to study given how uncommon it is to use radiation in conjunction with surgery. At our institution, before the advent of off-the-shelf endoprostheses, bone sarcomas (including osteosarcoma) were historically treated with low doses of radiation while the treatment team awaited the manufacturing of custom implants. Under modern treatment protocols, these patients would not be treated with radiation therapy; however, we believe this historical group of patients receiving radiation for bone and soft tissue sarcomas could be leveraged to identify an association between preoperative or postoperative radiation therapy and endoprosthesis survival and help inform surgeons and patients in situations where radiation therapy is still indicated.

Therefore, we asked: (1) Is receiving preoperative or postoperative radiation therapy in low or high doses for the treatment of bone or soft tissue malignancy of the lower extremities associated with decreased implant survivorship free from amputation or revision due to any cause? (2) Is receiving preoperative or postoperative radiation therapy in low or high doses for the treatment of bone or soft tissue malignancy of the lower extremities associated with decreased implant survivorship free from revision specifically due to aseptic loosening? (3) Is receiving preoperative or postoperative radiation therapy for the treatment of Ewing sarcoma of the femur specifically associated with decreased implant survivorship free from revision specifically due to aseptic loosening?

## Patients and Methods

### *Study Design and Setting*

This was a retrospective, comparative study using our institution's longitudinally collected endoprosthesis database. All patient evaluations and surgeries were performed by the orthopaedic oncology division at two hospitals that are part of a large, urban referral center. The operations were performed by a senior surgeon (JJE) with more than 20 years of experience and another surgeon (NMB) with more 10 years of experience whose practices exclusively involve the care of patients with primary malignant and benign bone and soft tissue tumors including skeletal metastatic disease.

This study covered a period from December 1, 1980 to December 31, 2019.

### *Patients*

Between 1980 and 2019, we treated 541 patients with primary cemented endoprostheses of the extremities. Limb salvage surgery was performed for patients in which curative tumor resection could be performed while preserving a functional extremity. Our institutional bias is to use endoprostheses instead of allograft in all patients due to superior immediate stability, functionality, and long-term durability. Cemented reconstructions were used exclusively at our institution from 1980 to 2013. From 2013 onward, cemented reconstruction has been the primary mode of reconstruction unless the patient had (1) anatomy preventing the ability to ream at least to 12.5 mm, (2) short residual bone stock that precluded a 120-mm-long stem, or (3) patient preference for biologic fixation with a compressive osseointegration device. The duration of follow-up time was determined from the date of surgery to the date of last documented follow-up.

Of those 541 patients, 8% (45 of 541) were excluded due to unknown radiation status, 3% (17 of 541) due to prior failed allograft, 15% (83 of 541) due to metastatic disease from a carcinoma, 1% (6 of 541) due to non-oncologic diagnosis, 4% (20 of 541) due to benign tumor diagnosis, 16% (87 of 541) due to upper extremity tumor location, 9% (49 of 541) due to not receiving chemotherapy, and 3% (14 of 541) due to expandable prostheses. Of the remaining 220 patients, 6% (13) were excluded because they did not have 2 years of follow-up and did not reach a study endpoint (death before 2 years or implant removal for any cause). No patients had surgery within the last 2 years of the study end date. In all, 207 patients met the inclusion criteria and were eligible for analysis. Of the final 207 patients included, 24% (50 of 207) have not been seen within last 5 years and were not known to reach a

study endpoint, and 16% (33 of 207) had not been seen in the last 10 years and were not known to reach a study endpoint. The mean follow-up of patients not seen in the last 5 and 10 years was 11.5 and 10 years, respectively. These patients were included, but their current status is not known with confidence, and we could not do an analysis comparing the missing to those for which we could account.

The primary outcome of interest was implant survival free from all-cause revision or amputation due to any cause. Revision surgery was defined as any surgery necessitating removal or replacement of the tibial or femoral stem. The complications necessitating revision or amputation were poor wound healing, aseptic loosening, implant breakage, periprosthetic fracture, deep infection, and tumor progression. Amputation was performed when a functional limb could not be preserved while performing a negative margin resection. The secondary outcome of interest was implant survival free from revision or amputation specifically due to aseptic loosening. The Kaplan-Meier survivorship curves were generated with death treated as a competing risk. A log-rank test was used to identify differences in survivorship between the patients who had radiation and those who did not receive radiation. Multivariate regression was used to identify factors associated with decreased implant survival. All variables were included in a univariate, exploratory analysis and were included in the multivariate analysis if $p < 0.05$. An odds ratio was used to determine relative effect size.

Patients were included in the radiation group if they received radiation to the extremity either preoperatively or postoperatively. Radiation doses above 3000 cGy were classified as high dose and doses between 1750 to 3000 cGy were classified as low dose. All patients with osteosarcoma were treated with low-dose radiation while awaiting implant manufacturing to decrease the risk of local recurrence through the year 1990. This is not consistent with our modern treatment paradigms, which are based on surgery and chemotherapy exclusively. As it relates to the extremity tumors in this study, we also utilize radiation for Ewing sarcoma in the setting of close or positive resection margins. All patients who received radiation therapy also received chemotherapy. To reduce the confounding effects of chemotherapy on endoprosthesis survivorship, we decided to remove all patients who received no chemotherapy ($n = 40$). These 40 patients also did not receive any radiation therapy.

All treatment protocols are created in consultation with our sarcoma-specific tumor board. Demographic, oncologic, implant, and treatment characteristics were used in the multivariate regression analysis to identify factors associated with implant revision. These included patient gender, age, tumor type, tumor stage, radiation exposure, implant type, implant location, resection length, stem length, stem width, and implant fabrication (modular versus custom). Tumor stage was determined in accordance with the Enneking staging system [13]. The tumor dictates the amount of resection for all patients. At our institution, we template for a resection 2 cm into healthy bone to achieve a wide bone margin. The standard cemented stem length is 120 mm or 127 mm depending on which implant manufacturer was utilized. This is selected to both achieve optimal implant stability while still preserving as much native bone as possible in the event the implant needs to be revised. The diameter is dictated by the intramedullary canal size. We ream until an appropriate amount of cortical chatter is felt and heard. We then cement in a stem that permits a 1- to 2-mm cement mantle on all sides plus a 2-cm cement pedestal. The progression from custom to modular implants occurred around 1990, and with the advent of that technology, modular implants have almost exclusively been used at our institution except in rare situations, such as extremely young patients who may benefit from custom small-diameter stems or in short, cemented stems where custom cross-pins have been added.

### *Participants' Baseline Data*

Of the patients who received radiation, 93% (68 of 73) had documentation of their radiation dose and were included in the low-dose (67% [49 of 73]) and high-dose (26% [19 of 73]) radiation groups (Table 1). The mean age for the patients who did not receive radiation was 26 ± 17 years and the mean age for the patients in the low-dose and high-dose radiation groups were 29 ± 17 years and 14 ± 7 years, respectively. The incidence of local recurrence and death due to sarcoma did not differ between groups. The tumor makeup of the patients in the nonirradiated group was primarily osteosarcoma (90% [121 of 134]) followed by soft tissue sarcoma (7% [10 of 134]) and Ewing sarcoma (2% [3 of 134]). For low-dose radiation, the most common tumor was osteosarcoma (78% [38 of 49]) followed by soft tissue sarcoma (22% [11 of 49]). The high-dose radiation group consisted primarily of patients with Ewing sarcoma (79% [15 of 19]) followed by osteosarcoma (16% [3 of 19]) and soft tissue sarcoma (5% [1 of 19]). The high-dose radiation group had a higher percentage of intercalary implants (21% [4 of 19]) compared with the low dose (2% [1 of 49]) and nonirradiated (1% [2 of 134]) groups and was included in the multivariate analysis. Because of the differences in tumor makeup, particularly with regard to Ewing sarcoma, a separate analysis was conducted for patients specifically with a diagnosis of Ewing sarcoma of the femur. The mean resection length for the patients in the nonirradiated, low-dose radiation, and high-dose radiation groups were 14 ± 8 cm, 18 ± 9 cm, and 16 ± 10 cm, respectively. Due to the differences in resection length, we

**Table 1.** Demographic, oncologic, and implant comparisons between the nonirradiated, all-radiation, low-dose radiation, and high-dose radiation cohorts

| | Nonirradiated (n = 134) | All radiation (n = 73)[a] | Low-dose radiation (n = 49) | High-dose radiation (n = 19) |
|---|---|---|---|---|
| Sex | | | | |
| Male | 57 (76) | 52 (38) | 51 (25) | 58 (11) |
| Female | 43 (58) | 48 (35) | 49 (24) | 42 (8) |
| Age in years | 26 ± 17 | 27 ± 14 | 29 ± 17 | 14 ± 7 |
| Disease-free interval in months | 25 ± 20 | 15 ± 22 | 13 ± 8 | 20 ± 42 |
| Amputation | 9 (12) | 4.1 (3) | 2 (1) | 5 (1) |
| Revision | 25 (33) | 34 (25) | 37 (18) | 26 (5) |
| Cause of revision/amputation | | | | |
| Poor wound healing | 0 (0) | 1.4 (1) | 0 (0) | 5 (1) |
| Aseptic loosening of cemented stem | 10 (13) | 21 (15) | 22 (11) | 21 (4) |
| Implant breakage | 12 (16) | 11 (8) | 10 (5) | 5 (1) |
| Deep infection | 3 (4) | 5 (4) | 6 (3) | 0 (0) |
| Tumor progression | 9 (12) | 0 (0) | 0 (0) | 0 (0) |
| Tumor type | | | | |
| Osteosarcoma | 90 (121) | 58 (42) | 78 (38) | 16 (3) |
| Ewing sarcoma | 2.2 (3) | 26 (19) | 0 (0) | 79 (15) |
| Soft tissue sarcoma | 7 (10) | 9 (12) | 22 (11) | 5 (1) |
| Tumor stage | | | | |
| IA/B | 1.5 (2) | 11 (8) | 16 (8) | 0 (0) |
| IIA/B | 93 (124) | 78 (57) | 73 (36) | 84 (16) |
| III | 6 (8) | 11 (8) | 10 (5) | 16 (3) |
| Endoprosthesis location | | | | |
| Femur | 74 (99) | 95 (69) | 96 (47) | 95 (18) |
| Tibia | 26 (35) | 5 (4) | 4 (2) | 5 (1) |
| Endoprosthesis type | | | | |
| Proximal femur replacement | 11 (15) | 26 (19) | 16 (8) | 47 (9) |
| Distal femur replacement | 61 (82) | 62 (45) | 78 (38) | 26 (5) |
| Proximal tibia replacement | 27 (36) | 5 (4) | 4.1 (2) | 5 (1) |
| Intercalary | 1.5 (2) | 7 (5) | 2 (1) | 21 (4) |
| Implant characteristics | | | | |
| Resection length in cm | 14 ± 8 | 17 ± 9 | 18 ± 9 | 16 ± 10 |
| Stem length in cm | 11 ± 4.6 | 12 ± 6 | 12 ± 3.9 | 11 ± 9 |
| Stem diameter in mm | 14 ± 2.1 | 15 ± 2.8 | 15 ± 2.5 | 16 ± 2.5 |
| Fabrication | | | | |
| Modular | 43 (58) | 25 (18) | 10 (5) | 47 (9) |
| Nonmodular | 57 (76) | 75 (55) | 90 (44) | 53 (10) |
| Follow-up time in years | 11 ± 9 | 13 ± 12 | 14 ± 13 | 10 ± 9 |
| Died of disease | 29 (39) | 47 (34) | 55 (27) | 37 (7) |
| Local recurrence | 7 (9) | 15 (11) | 18 (9) | 11 (2) |

Data presented as mean ± SD or % (n).

[a]In this study, 5 of 73 patients had documentation of radiation therapy, but no clarification of the dosage, thus we included them in the "all radiation" group but did not include them in the low-dose and high-dose groups.

controlled for it in the multivariate regression analysis along with other implant parameters including stem length and stem diameter. The percentages of nonmodular implants between the patients who were not irradiated, who received low-dose radiation, or high-dose radiation were 57% (76 of 134), 90% (44 of 49), and 53% (10 of 19), respectively (Table 1). The higher percentage of nonmodular implants in patients who received low-dose radiation is because this group of patients generally comes from the older osteosarcoma treatment group. We controlled for this in the multivariate analysis.

### *Primary and Secondary Study Outcomes*

Our primary study goal was to compare lower extremity endoprosthesis survival free from amputation or revision for any cause between patients who received no radiation, low-dose radiation, and high-dose radiation therapy. To achieve this, we collected data on patients' demographics, diagnosis, treatment, prosthesis characteristics, and clinical indications for reoperation. We stratified our study population by radiation status and compared endoprosthesis survival between groups. Subsequently, a multivariate analysis was done to control for confounding effects due to differences between these groups of patients. The causes of reoperation were classified as poor wound healing, aseptic loosening of the cemented stem, implant breakage, deep infection, or tumor progression. Revision surgery was defined as any reoperation that involved removal or replacement of a stemmed component. Prosthesis survival was defined as the date of surgery to date of revision or amputation.

Our secondary research goals were to compare lower extremity endoprosthesis survival free from amputation or revision specifically due to aseptic loosening. Aseptic loosening was defined by the operating surgeon based on patient history and radiographs. This was confirmed intraoperatively when motion between the bone-cement or cement-implant interface could be induced manually. Preoperative infectious workup and intraoperative cultures were confirmed negative for all patients defined as having aseptic loosening. We performed the same statistical analyses as for the primary study goal, but this time looking specifically at survival to aseptic loosening of the prosthesis. We also evaluated the association between radiation exposure and implant survival specifically in patients with a diagnosis of Ewing sarcoma of the femur.

### *Ethical Approval*

Ethical approval for this study was obtained from the University of California Los Angeles Office of the Human Research Protection Program (IRB#10-001857-AM-00031).

### *Statistical Analysis*

We compared patients who received radiation with those who did not. Kaplan-Meier survivorship curves, stratified by radiation status, were created with amputation or revision as the endpoint. These were generated with patient death as a competing risk. We used the log-rank test to identify differences in survivorship between the patients who received radiation and those who did not receive radiation. We performed multivariate Cox regression for developing implant failure using gender, age, radiation status, resection length, stem length, stem width, implant modularity, and implant location as candidate variables. For statistical analysis, we grouped diagnoses of undifferentiated pleomorphic sarcoma, fibrosarcoma, desmoid, leiomyosarcoma, spindle sarcoma, soft tissue/synovial sarcoma, and rhabdomyosarcoma as soft tissue sarcomas. All patients with soft tissue sarcomas were treated with endoprostheses due to initial bone involvement, not subsequent bone fracture after radiation. We used ORs with 95% confidence intervals (CIs) to determine relative effect size among the factors associated with decreased implant survival.

All statistical analyses were performed with SPSS Version 25.0 (IBM Corp) and Stata/BE Version 17.0 (StataCorp). All p values were two-sided, and $p < 0.05$ was considered significant.

## Results

### *Radiation and Survivorship Free From Amputation or Revision for Any Reason*

Patients who received radiation before or after lower extremity tumor resection and reconstruction had no difference in all-cause implant survival compared with patients who did not receive radiation (Fig. 1). The mean implant survival time for patients who did not receive radiation was 18.3 years (95% CI 15.4 to 21.3), and the mean implant survival times for patients who received low- and high-dose radiation were 19.1 years (95% CI 14.5 to 23.7; $p = 0.59$) and 13.8 years (95% CI 8.2 to 19.5; $p = 0.65$), respectively (Fig. 1).

On multivariate analysis, age younger than 18 years at the time of surgery was associated with poorer all-cause implant survival (OR 2.2 [95% CI 1.2 to 4.2]; $p = 0.02$) compared with patients older than 18 years at the time of surgery (Table 2). Intercalary implant design was associated with poorer all-cause implant survival (OR 36 [95% CI 4.9 to 269]; $p < 0.001$) compared with nonintercalary designs (Table 2).

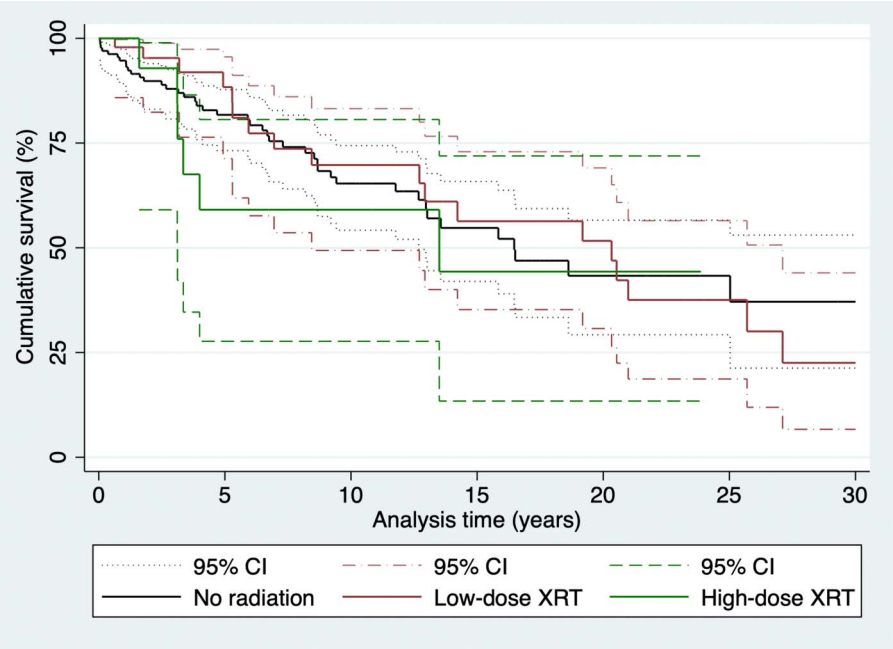


**Fig. 1** This graph shows the Kaplan-Meier survival curve for implant survivorship free from amputation or revision due to any reason stratified by radiation therapy status, adjusted for the competing risk of death; XRT = radiotherapy. A color image accompanies the online version of this article.

*Radiation and Survivorship Free From Revision due to Aseptic Loosening*

Patients who received high-dose radiation before or after lower extremity tumor resection and reconstruction had decreased mean time to revision and 5-year survivorship free from revision for aseptic loosening (Fig. 2). The mean implant survival free from amputation or revision for aseptic loosening for patients who did not receive radiation was 27.1 years (95% CI 24.1 to 30.1) while the mean implant survival for patients who received low- and high-dose radiation were 24.1 years (95% CI 19.1 to 29.1; p = 0.34) and 16.4 years (95% CI 10.6 to 22.2; p = 0.01), respectively (Fig. 2). Patients who received high-dose radiation had decreased 5-year implant survivorship free from revision due to aseptic loosening (73% [95% CI 44% to 89%]) compared with patients who did not receive radiation (95% [95% CI 90% to 99%]; p = 0.01). The 5-year implant survivorship free from amputation or revision due to aseptic loosening for patients who received low-dose radiation was 95% (95% CI 81% to 99%; p = 0.9).

**Table 2.** Multivariate Cox regression for survival free from amputation or revision for any reason

| | OR (95% CI) | p value |
|---|---|---|
| Age younger than 18 vs age older than 18 | 2.2 (1.2-4.2) | 0.02 |
| Male compared with female | 1.4 (0.7-2.5) | 0.31 |
| Low-dose radiation vs no radiation | 0.9 (0.4-1.9) | 0.74 |
| High-dose radiation vs no radiation | 0.4 (0.1-2) | 0.29 |
| Resection length in cm | 1 (1-1.1) | 0.22 |
| Stem length in cm | 1 (0.9-1) | 0.40 |
| Stem diameter in mm | 1.1 (1-1.3) | 0.18 |
| Modular fabrication vs nonmodular | 0.6 (0.3-1.3) | 0.20 |
| Intercalary implant design vs nonintercalary | 36 (4.9-269) | < 0.001 |
| Soft tissue sarcoma diagnosis vs nonsoft tissue sarcoma | 3.1 (1-10) | 0.06 |

On multivariate analysis, low-dose (OR 1.4 [95% CI 0.4 to 5.1]; p = 0.6) and high-dose (OR 0.7 [95% CI 0.1 to 8.6]; p = 0.7) radiation were not associated with decreased implant survival free from revision for aseptic loosening. Every 1-cm increase in resection length was associated with decreased implant survival free from revision for aseptic loosening (OR 1.1 [95% CI 1.0 to 1.2]; p = 0.02) (Table 3). Intercalary implant design was associated with decreased implant survival compared with nonintercalary design (OR 194 [95% CI 7.7 to 4886]; p < 0.001) (Table 3).

*Radiation and Survivorship Free From Revision Because of Aseptic Loosening in Patients With a Diagnosis of Ewing Sarcoma of the Femur*

Patients with a diagnosis of Ewing sarcoma of the femur who received high-dose radiation to the femur before or after

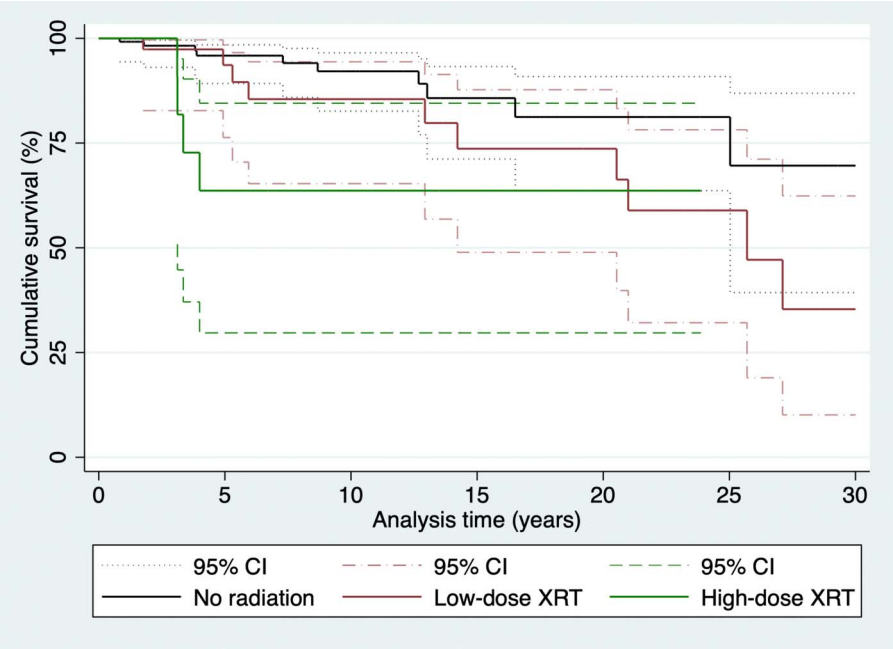


**Fig. 2** This graph shows the Kaplan-Meier curve for implant survivorship free revision specifically due to aseptic loosening stratified by radiation therapy status, adjusted for the competing risk of death. A color image accompanies the online version of this article.

tumor resection and reconstruction had no difference in survivorship free from revision due to aseptic loosening (Fig. 3). The 5-year implant survival for patients who did not receive radiation (100% [95% CI 100% to 100%]) was no different compared with patients who received high-dose radiation (71% [95% CI 35% to 90%]; p = 0.56) (Fig. 3).

## Discussion

Preoperative or postoperative radiation therapy in combination with limb salvage surgery may be used for certain patients to treat close surgical margins or decrease rates of local recurrence. Radiation has known detrimental effects on bone including fractures, infection, delayed wound healing, and impaired osseointegration, which may diminish endoprosthesis survivorship. Although prior studies have documented decreased endoprosthesis survival and higher infection rates in patients with radiation exposure, results are inconsistent [9, 15, 16, 22, 23, 33]. Additionally, the association of early revision for aseptic loosening in patients exposed to radiation is not well described in other reports [9, 15, 16, 20, 22, 23, 25, 29, 33]. We performed a retrospective study of 207 patients to examine the association of radiation and endoprosthesis survival to amputation or revision surgery and whether there was an association with decreased prosthesis survival. We found that lower extremity endoprostheses exposed to high-dose radiation (more than 3000 cGy) have a decreased mean survival time and decreased 5-year survival to amputation or revision due to aseptic loosening compared with endoprostheses with no radiation exposure. Low-dose radiation (less than 3000 cGy) did not show any association. Age younger than 18 years old at the time of surgery and intercalary implant design was associated with decreased prosthesis survival to amputation or revision for any reason when controlling for confounding variables such as patient gender, age, and tumor resection length as well as implant variables such as stem length, stem diameter, modular versus nonmodular implant, and location. Greater resection length and intercalary implant design

**Table 3.** Multivariate Cox regression for implant survival free from amputation or revision due to aseptic loosening

| | OR (95% CI) | p value |
|---|---|---|
| Age younger than 18 vs age 18 years or older | 0.7 (0.2-2) | 0.52 |
| Male vs with female | 2.6 (0.8-8.4) | 0.12 |
| Low vs no radiation | 1.4 (0.4-5.1) | 0.58 |
| High vs no radiation | 0.7 (0.1-8.6) | 0.75 |
| Resection length in cm | 1.1 (1.0-1.2) | 0.02 |
| Stem length in cm | 1 (0.9-1.1) | 0.57 |
| Stem diameter in mm | 1 (0.7-1.3) | > 0.99 |
| Modular fabrication vs nonmodular | 1.3 (0.3-5.7) | 0.74 |
| Intercalary implant design vs nonintercalary | 194 (7.7-4886) | < 0.001 |
| Soft tissue sarcoma diagnosis vs nonsoft tissue sarcoma | 1.5 (0.2-15) | 0.71 |

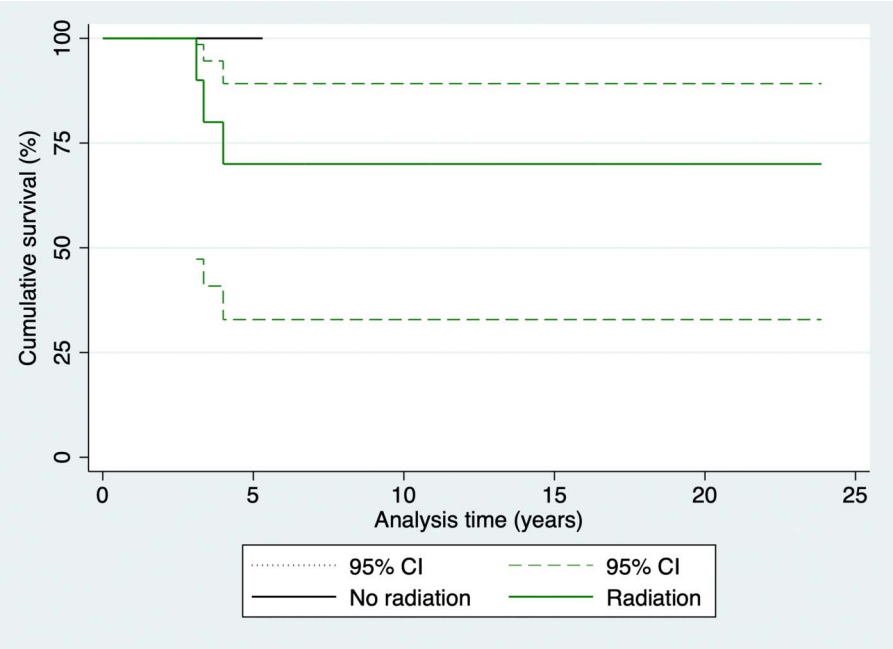


**Fig. 3** This graph shows the Kaplan-Meier curve for implant survivorship free from revision specifically due to aseptic loosening in patients with Ewing sarcoma of the femur stratified by radiation therapy status, adjusted for the competing risk of death. A color image accompanies the online version of this article.

were associated with decreased prosthesis survival to revision for aseptic loosening when controlling for the same variables. Although the use of radiation in conjunction with resection and reconstruction with a prosthesis is rare, radiation is still used in Ewing sarcoma with positive margins or local recurrence and after prosthetic reconstruction in patients with myeloma or bone metastasis after resection of periarticular destructive tumors. Based on our findings, we think surgeons may consider closer assessment for clinical and radiographic signs of aseptic loosening in patients who received preoperative or postoperative radiation doses over 3000 cGy, particularly within the first 5 years after surgery, to allow for early detection and possible treatment, if indicated. Surgeons may also consider the use of constructs that have increased resistance to aseptic loosening such as cross-pin or side plate fixation [7].

*Limitations*

This study has a number of limitations. First, this is a retrospective study and can only identify associations between our variables of interest and not cause and effect. The data loss and bias that can often accompany retrospective studies is mitigated somewhat in that our endoprosthesis database is longitudinally maintained. Transfer bias is certainly a weakness of this study, particularly because it spanned such a long period of time. Twenty-four percent (50 of 207) of patients had not been seen within the last 5 years of the study endpoint and were not known to have reached a study endpoint, and 16% (33 of 207) had not been seen in the last 10 years and were not known to reach a study endpoint. It is possible that the patients lost to follow-up experienced complications and sought care elsewhere, and their status could not be known with confidence beyond their last documented follow-up. However, the mean follow-up of these patients at 5 and 10 years was relatively long at 11.5 and 10 years, respectively, and thus there is likely minimal effect on our findings as most incidences of aseptic loosening occurred before 5 years in the radiation group. Of the patients not seen in the last 5 years, 78% (39 of 50) did not receive radiation therapy compared with 76% (25 of 33) of patients not seen in the last 10 years. Although these patients lost to follow-up at 5 and 10 years would be censored in our survival analysis beyond their last known follow-up, there is still a risk of underestimating the incidence of complications, particularly beyond 10 years. Specific to this study, there is limited information available on the amount of time between radiation and surgery or if radiation was used in the preoperative or postoperative settings. Although the timing of radiation may affect acute complications of surgery, including fracture, infection, and wound healing, the primary outcome of interest in this study was implant revision occurring several years after surgery and is more

likely to depend on whether radiation was used at all and at what dose than when exactly it was used. Our inability to differentiate preoperative and postoperative radiation still remains an important limitation to consider when interpreting our results. Additionally, we were unable to determine the volume of irradiated tissue and this could have confounding effects on our results. Second, our database has been collected over 40 years, and there have been changes in surgical and treatment techniques over that period that may lead to selection bias. Cemented reconstructions were used exclusively at our institution from 1980 to 2013. From 2013 onward, cemented reconstruction has been the primary mode of reconstruction unless the patient had (1) anatomy preventing the ability to ream to at least 12.5 mm, (2) short residual bone stock that precluded a 120-mm-long stem, or (3) patient preference for biologic fixation with a compressive osseointegration device. The duration of follow-up time was determined from the date of surgery to the date of last documented follow-up. The transition from custom to modular implant designs, for example, represents a crucial change because custom implant designs have been documented to have higher revision rates compared with the modern, modular implants [30]. However, these factors were controlled for in our multivariate analyses, and the 40-year experience represents a strength in duration of follow-up. Changes in radiotherapy techniques over time and differences in technique between patients may also confound our results, and this should be considered when interpreting our results. With regard to changes in treatment protocols, our institution used to treat osteosarcoma with radiation to reduce local recurrence during the development of limb salvage surgery techniques. The use of radiation in the treatment of osteosarcoma at our institution was phased out around 1990 when it was decided that the risks of radiation outweighed the theoretical benefits it could have on reducing local recurrence. The patients with osteosarcoma in the low-dose radiation group herein represent an older group of patients in our database. This may also be reflected in the longer follow-up time seen in the patients who were treated with low-dose radiation. Radiation technologies have also evolved over the course of the study period. Although we controlled for confounders in the regression model, it is still possible that other heterogeneity in surgical technique or treatment protocols was not sufficiently captured. Differences in the quality of cementing and stem filling ratio, the presence of a collar for extracortical bridging, and the use of a rotating hinge would all impact the incidence of aseptic loosening. Loosening of an endoprostheses may require long follow-up to observe, so although treatment changes may confound results, we feel the long study period is one of our strengths. There is a high degree of heterogeneity in tumor type and location in our patients, specifically with regard to the inclusion of soft tissue sarcoma. If an endoprosthesis was used to reconstruct a limb after soft tissue sarcoma resection, as in situations where the bone or joint could not be spared due to tumor size or location, then the radiation field also involved the reconstruction. For this reason, we felt it important to include these implants just like those used to reconstruct primary bone histologies since they share a common radiation exposure. Additionally, we felt it necessary to expand our study group to several locations and tumor types to maximize statistical power. We conducted a subanalysis of Ewing sarcoma of the femur in an effort to have a homogenous group, but this sample size was quite small and may have been underpowered to detect any differences in implant survival between patients who did and did not receive radiation therapy. This underscores the inevitability of some heterogeneity in any study of patients with sarcoma that will have sufficient statistical power. Although our study was focused on the lower extremity, there is still heterogeneity with the types of implants used, which include proximal femur, distal femur, proximal tibia, and intercalary endoprosthesis. Intercalary implants may be at an increased risk of aseptic loosening, although the reported rates are variable [1, 5]. They were included in this study because they represent a large portion of our Ewing sarcoma subanalysis (18% [4 of 22]) and high-dose radiation group (21% [4 of 19]) and may represent a particularly high-risk group worth reporting on. We have attempted to control for their confounding effects in our multivariate analysis, but their inclusion certainly adds heterogeneity within our study. We controlled for tumor location and surgical variables like resection length, stem length, and stem diameter in our regression model, and the consistent use of cemented stems represents a critical consistency in fixation method.

### *Radiation and Survivorship Free From Amputation or Revision for Any Reason*

Our study found that endoprostheses exposed to radiation do not have decreased survivorship to amputation or revision from any cause. However, other published studies have found a negative effect of radiation therapy on endoprosthesis survivorship [15, 22, 23, 33]. Jeys et al. [23] found radiation therapy to have a decreased 10-year survival (29%) compared with the no radiation therapy group (58%). In contrast, our 10-year implant survival between the low-dose (71%), high-dose (68%), and no radiation (66%) groups showed no differences. When comparing that study with ours, some key differences should be noted. First, the study by Jeys et al. [23] found a higher incidence of deep periprosthetic infection that could account for the decreased implant survivorship, although they did not list

the reasons for all revisions. We did not observe a difference in infection attributable to radiation exposure, similar to other studies [9]. The reason for this difference is likely multifactorial. Although one explanation for the discrepancy is an actual difference in infection incidence, it may partly reflect different definitions of infection complications, as debridement for superficial surgical site infection that did not result in cemented implant revision was not captured as an implant revision in our database because the endoprosthesis was not revised in these patients. All-cause revision gives a broad view of how radiation exposure affects implant survival, but there are more specific reasons why an implant is revised, and thus we sought to explore the different indications for revision individually. Based on these findings, patients with preoperative or postoperative radiation therapy should not be treated with any different infection mitigation strategies such as different perioperative antibiotic regimens as compared with those for non-irradiated patients.

### *Radiation and Survivorship Free From Amputation or Revision due to Aseptic Loosening*

Our study showed that higher radiation doses (> 3000 cGy) were associated with a decreased implant survival time to amputation or revision due to aseptic loosening. Aseptic loosening has been shown to be a primary cause of endoprosthesis revision in other reports [19, 31], so it is important to understand the factors that affect rates of aseptic loosening if we hope to improve the long-term implant durability. As sarcoma survivorship increases the number of endoprostheses with long follow-up, we can expect endoprosthesis revision due to aseptic loosening to become increasingly prevalent as well. Although prior studies examining radiation therapy have focused on its association with endoprosthesis revision due to periprosthetic infection, little attention has been paid to aseptic loosening [16, 22, 23]. We identified one study that found no association between radiation and survival of cemented megaprostheses, although this study was limited by a relatively a small group of 10 patients with radiation exposure [9]. Cemented implants have traditionally been thought to be resistant to the harmful effects of radiation on the osseointegration necessary for successful uncemented implants, but the results of this study suggest that there is still an association between aseptic loosening and cemented implants after radiation treatment. A recent meta-analysis looking at joint arthroplasty has examined this association and showed similar findings: Patients with a history of pelvic irradiation undergoing total hip replacement had higher rates of aseptic loosening in both cemented and uncemented acetabular cups [26]. Bone cement causes thermal damage to surrounding bone as it cures, initiating a remodeling process that relies on the formation of fibrovascular tissue, which is eventually replaced by bone marrow elements leading to new bone formation by apposition of lamellae at the bone-cement interface, which then results in durable fixation [37]. This phase of stabilization at the bone-cement interface is highly sensitive. Repeated cell damage gives rise to granulomatous tissue and stimulates osteoclastic osteolysis, bone resorption, and subsequent impairment of the anchors for implant fixation, which may lead to implant loosening [11, 12, 37]. All patients with aseptic loosening in the high-dose radiation group exhibited early loss of fixation occurring within 5 years of their operation. It is possible that this early loss of fixation is due to the toxic effects of high-dose radiation therapy causing impairment of the bone-cement stabilization process outlined above. We also found that greater resection length and intercalary implant designs were associated with early revision due to aseptic loosening. Greater resection length is known to be associated with earlier aseptic loosening, but it is dictated by the tumor and not a modifiable factor for surgeons [24, 36]. There is a theoretical risk of increased aseptic loosening in intercalary implants because there are two stemmed components that could loosen, although reported rates range from 14% to 50% [1, 5]. These variables, along with the use of radiation therapy for positive margins or local recurrence, are not modifiable factors as they are dictated by the tumor. However, surgeons may consider closer assessment for clinical and radiographic signs of aseptic loosening in patients who received preoperative or postoperative radiation doses of more than 3000 cGy for earlier detection and potential treatment if indicated, particularly within the first 5 years from surgery. They should also pay close attention to early signs of aseptic loosening in patients whose tumors have larger resection lengths or intercalary designs. In patients felt to be at higher risk of loosening of cemented endoprostheses, such as those reconstructed with intercalary implants or those treated with high-dose radiation, surgeons should consider implant designs with adjuvant fixation strategies such as custom cross pins [7]. Future assessment of this subject would benefit from a well-designed, prospective study with homogeneity in tumor type, such as Ewing sarcoma, and implant design.

### *Radiation and Survivorship Free From Amputation or Revision due to Aseptic Loosening in Patients With a Diagnosis of Ewing Sarcoma of the Femur*

Our study found no association between preoperative or postoperative radiation therapy and decreased

survivorship from reoperation due to aseptic loosening in patients with Ewing sarcoma of the femur. At our institution, appendicular Ewing sarcoma is treated with chemotherapy and surgical resection. Radiation is typically reserved for patients who get a local recurrence or positive tumor margins after resection and reconstruction. Although we found no association between radiation therapy and implant survival free from reoperation due to aseptic loosening, this may represent a Type II error. Because these tumors are rare and their location and treatment modalities vary, a multi-institution retrospective study may be beneficial and provide sufficient statistical power, even though this would introduce more institution-specific biases with regard to surgeon technique and treatments.

*Conclusion*

Radiation therapy with doses greater than 3000 cGy to the resection site during treatment for bone and soft tissue malignancies of the lower extremities is associated with decreased survival of lower extremity cemented endoprostheses due to aseptic loosening. Greater resection length and intercalary implant designs are also associated with decreased survival due to aseptic loosening. Although most patients who received radiation for osteosarcoma represent a historical group of patients that would not receive radiation today under the same circumstances, the effects of radiation on bone are consistent and the results of this study may apply to scenarios where radiation is still used, such as Ewing sarcoma with positive margins or local recurrence and after prosthetic reconstruction in patients with myeloma or bone metastasis after resection of periarticular destructive tumors. Surgeons may consider closer monitoring for early clinical and radiographic signs of aseptic loosening in patients who received high-dose radiation, particularly if they had larger bone resection or have intercalary implants. These patients may also benefit from constructs that have increased resistance to aseptic loosening such as cross-pin or side plate fixation. This study has several limitations, and the association between radiation and aseptic loosening should be further studied with larger studies with homogeneity in tumor diagnosis and modern prostheses. Close attention should be paid to confounding factors on aseptic loosening such as radiotherapy technique, volume of tissue irradiated, and prosthetic design. The dose-dependent relationship between radiation and bone-related complications such as implant loosening may also be further explored through controlled, laboratory-based, biomechanical studies. Orthopaedic oncologists and radiation oncologists should work together to understand how to best mitigate the harmful effects of radiation treatment on the healthy bone that will be spared by tumor resection to improve the durability of limb reconstruction.

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